## REVIEW ARTICLE

### DRUG THERAPY

ALASTAIR J.J. WOOD, M.D., *Editor*

# THEOPHYLLINE IN ASTHMA

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THEOPHYLLINE has been a popular medication for asthma for over 50 years. However, the introduction of newer pharmacologic agents, concern about the toxicity of theophylline, and recommendations in widely disseminated guidelines have recently contributed to its decreased use. In this review we reassess the role of theophylline in the pharmacotherapy of asthma and specifically address three pivotal questions: What are the data justifying its continued use? What are its risks? What is its role in the treatment of patients with asthma?

## HISTORY

Although first used as intravenous therapy for acute asthma[1] and then as an oral medication in fixed doses in combination with ephedrine,[2] the chief current use of theophylline began in the early 1970s with reports demonstrating its efficacy as preventive monotherapy for chronic asthma.[3,4] Subsequent definition of its pharmacodynamics and pharmacokinetics provided information that allowed safer and more effective use.[5,6] These data led also to the development of slow-release formulations that compensated for the rapid absorption and elimination of theophylline,[7] and the development of rapid assays made therapeutic drug monitoring readily available.[8] By 1980, slow-release theophylline had become a leading medication for asthma. Despite the expanding array of newer drugs, the recent recognition that theophylline has antiinflammatory and immunomodulatory actions has stimulated further interest in its potential for treating chronic asthma.[9]

## PHARMACOLOGIC ACTIONS

Though it has traditionally been classified as a bronchodilator, the ability of theophylline to control chronic asthma is disproportionately greater than is explainable by its relatively small degree of bronchodilator activity.[3,4,10-16] Theophylline in fact has immunomodulatory,[16] antiinflammatory,[17,18] and bronchoprotective[19-22] effects that potentially contribute to its efficacy as a prophylactic antiasthma drug.

Theophylline down-regulates the function of inflammatory and immune cells in vitro and in vivo in animals with airway inflammation.[23,24] In patients with allergic asthma, it attenuates the late-phase increase in airway obstruction and airway responsiveness to histamine[17] and decreases allergen-induced migration of activated eosinophils into the bronchial mucosa.[18] Moreover, discontinuation of theophylline in 27 adults with severe chronic asthma who were receiving high doses of inhaled corticosteroids resulted in increased symptoms of asthma, especially at night, and an increase in the number and activation of T lymphocytes in airway mucosa.[16] The decrease in lung function that occurs at night in many patients with asthma is reduced by theophylline, and this reduction has been associated with a decrease in both the percentage of neutrophils and the level of stimulated leukotriene $B_4$ released from macrophages in bronchoalveolar-lavage fluid obtained early in the morning.[25]

In patients with mild asthma, theophylline reduces airway responsiveness to histamine,[19] methacholine,[19] allergen,[17] sulfur dioxide,[20] distilled water,[21] toluene 2,4-diisocyanate,[26] and adenosine.[27] Although the degree of attenuation is relatively small for most of these bronchoconstrictors, theophylline can completely inhibit airway responsiveness to exercise at a serum concentration of $\geq 15$ $\mu$g per milliliter[22] — a value in the upper half of the range (10 to 20 $\mu$g per milliliter) that provides optimal control of chronic asthma.[3,5,28,29] None of these bronchoprotective effects correlate well with the degree of bronchodilation produced by theophylline before the challenge. For substances such as methacholine and histamine that directly stimulate the contraction of bronchial smooth muscle, the bronchoprotection may be effected by direct inhibition of smooth-muscle contraction. In contrast, attenuation of the early response to allergen or exercise by theophylline may involve inhibition of the release of leukotrienes from the airways,[30] attenuation of the effects of leukotriene $D_4$ at its receptor,[31] or blocking of adenosine-induced enhancement of mediator release from mast cells.[32]

These findings suggest but do not establish that theophylline has antiinflammatory, immunomodulatory, and bronchoprotective effects that contribute to its efficacy as preventive therapy for chronic asthma. Theophylline also decreases fatigue in diaphragmatic muscles,[33] increases mucociliary clearance,[34] acts centrally to block the decrease in ventilation that occurs with sustained hypoxia,[35] and decreases microvascular leakage of plasma into the airways.[36] Although they are unlikely to be important in chronic asthma, some of these actions may provide a rationale for the addition of theophylline to the treatment of acute asthma that is unresponsive to the vigorous use of inhaled $\beta_2$-adrenergic

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agonists and systemically administered corticosteroids. These actions may also be relevant to the use of theophylline in other clinical situations such as the treatment of chronic obstructive pulmonary disease or apnea of prematurity, or weaning of premature infants from ventilators.

## Molecular Mechanisms of Action

Although several molecular mechanisms have been proposed to explain the actions of theophylline, nonspecific inhibition of phosphodiesterase isoenzymes and nonselective antagonism of specific cell-surface receptors for adenosine are the only ones known to occur at clinically relevant drug concentrations. Theophylline increases the intracellular concentration of cyclic nucleotides in airway smooth-muscle and inflammatory cells by inhibiting phosphodiesterase-mediated hydrolysis of these nucleotides. Inhibition of phosphodiesterase types III and IV relaxes smooth muscles in pulmonary arteries and airways,[37] whereas the antiinflammatory or immunomodulatory actions probably result from inhibition of the type IV isoenzymes.[24] Theophylline's bronchoprotective effects against the early response to bronchoconstriction induced by antigen and leukotriene $D_4$ appear to be mediated by a common, but unknown, molecular mechanism that does not involve the inhibition of phosphodiesterase or the antagonism of adenosine receptors.[31] Centrally mediated stimulation of respiration,[38] nausea and vomiting,[39] and ventricular arrhythmias that result from toxic serum concentrations of theophylline are probably mediated by phosphodiesterase inhibition, although the isoenzymes involved have not been defined.

It is unlikely that antagonism of adenosine receptors is involved in the bronchodilator action of theophylline. Enprofylline, a methylxanthine that does not antagonize adenosine receptors, is a more potent inhibitor of phosphodiesterase and a more potent bronchodilator than theophylline, whereas 8-phenyltheophylline, a potent adenosine-receptor antagonist that does not inhibit phosphodiesterase, does not relax bronchial smooth muscle in vivo.[31] However, nonspecific antagonism of adenosine receptors appears to be the mechanism by which theophylline increases ventilation during hypoxia, decreases fatigue in diaphragmatic muscles, and decreases adenosine-stimulated mediator release from mast cells.[9] Some adverse effects of theophylline, such as increased psychomotor activity, sinus tachycardia, gastric acid secretion, diuresis, and antagonism of the $\gamma$-aminobutyric acid–benzodiazepine receptor complex in the brain, probably also result from antagonism of adenosine receptors.[9] This mechanism also decreases cerebral blood flow,[40] although this effect is small and not clinically important.

## Comparison with Alternative Drugs

Whichever pharmacologic actions can be attributed to the clinical effect of theophylline in the treatment of asthma, the final rationale for its use must be based on therapeutic efficacy and safety in relation to the alternatives.

### Intervention for Relief of Acute Symptoms

In a controlled clinical trial involving 44 adults who presented with acute asthma in an emergency department, theophylline (given intravenously in the form of aminophylline) was no more effective than placebo when added to vigorous therapy with inhaled $\beta_2$-adrenergic agonists and systemic corticosteroids.[41] In patients with severe exacerbations of asthma requiring hospitalization, data on the value of adding theophylline are conflicting.[42-45] In one study of 39 hospitalized adults, the addition of theophylline to inhaled albuterol and oral prednisone was not beneficial.[42] In contrast, another study of 21 adults found that the addition of theophylline to inhaled albuterol and intravenous methylprednisolone resulted in greater improvement in forced expiratory volume in one second at 3 and 48 hours and a decreased need for rescue therapy with inhaled albuterol; there was no accompanying increase in the frequency of adverse effects.[43] With the use of the same protocol, theophylline was not beneficial in children treated at the same institution.[44] The difference in results was thought to be the more vigorous use of inhaled $\beta_2$-agonist drugs in treating the children.

Theophylline thus appears superfluous for the routine treatment of acute exacerbations of asthma in patients who are receiving optimal therapy with inhaled $\beta_2$-adrenergic agonists and corticosteroids. However, patients with respiratory failure were excluded from these studies for ethical reasons, and the addition of theophylline to drug therapy may be justified for patients with severe acute symptoms that do not respond rapidly to these other measures.

### Maintenance Therapy for Chronic Asthma

Cromolyn sodium was the first medication to be introduced exclusively for the prevention of the symptoms of asthma. In a multicenter trial of theophylline and cromolyn given for one month each to patients with severe chronic asthma, theophylline resulted in more days without symptoms.[10] In subsequent studies of patients with milder disease, the efficacy of cromolyn and theophylline was similar; however, those studies used a 20-mg dose of nebulizer solution or a dry-powder inhaler (Spinhaler) formulation of cromolyn administered four times daily.[46] In the United States the 20-mg dry-powder inhaler has been replaced by a metered-dose inhaler that delivers 1 mg per puff; the latter delivers less cromolyn to the lungs than the nebulizer, the dry-powder inhaler, or a metered-dose inhaler available outside the United States that delivers 5 mg per puff.[47,48] Although studies comparing nedocromil with theophylline are lacking, data in the package insert of nedocromil indicate that its efficacy is no greater than that of cromolyn.

In comparisons with selective $\beta_2$-adrenergic agonists,

theophylline was more effective than oral metaproterenol,[12] oral slow-release terbutaline,[49] and inhaled albuterol given four times daily.[13] A new ultra-long-acting inhaled $\beta_2$-adrenergic agonist, salmeterol, is more effective than albuterol as maintenance therapy for chronic asthma.[50] In a crossover study of adults (median age, 51 years),[51] two weeks of salmeterol was more effective than two weeks of theophylline, but only 98 of the 141 patients completed the trial and more than half the patients had serum theophylline concentrations below the range of 10 to 20 $\mu$g per milliliter within which efficacy is most likely to be maximal.[3,5,28,29] Although several large trials have reported sustained bronchodilation and clinical efficacy with the long-term use of salmeterol,[50] there is concern about the loss of the drug's bronchoprotective effect after challenge with methacholine,[52] exercise,[53] and allergen inhalation[54] after as little as two weeks. In contrast, attenuation of airway responsiveness to exercise is sustained with theophylline.[55]

In a randomized, blinded, parallel study comparing twice-daily slow-release theophylline and inhaled beclomethasone dipropionate in 195 children with asthma described as mild to moderate, symptom control and the decrease in airway hyperresponsiveness were similar, but the beclomethasone-treated patients used bronchodilators less often and needed fewer courses of systemic corticosteroids.[56] However, serum drug concentrations were usually below the range of 10 to 20 $\mu$g per milliliter in the theophylline group. The patients receiving theophylline reported more minor side effects but grew more rapidly during the 12-month study period. In a randomized crossover study of eight adults with asthma who were treated with twice-daily slow-release theophylline (mean serum concentration, 11.9 $\mu$g per milliliter) and inhaled budesonide (0.4 mg twice daily), each for six weeks, the frequency of rescue therapy with $\beta_2$-adrenergic agonists and daily peak expiratory flow rates during the study were similar with the two treatments, as were the results of spirometry, studies of carbachol bronchoprovocation and mucociliary clearance, and cytologic analysis of bronchoalveolar-lavage fluid performed at the end of each treatment period.[57]

Theophylline adds substantial clinical benefit to a regimen consisting of either an inhaled corticosteroid or an oral prednisone given every other morning[11,14-16] (Fig. 1), even among patients receiving 1500 $\mu$g of beclomethasone per day.[16] The benefit includes decreased symptoms, improved exercise tolerance, and a decreased need for both inhaled bronchodilators and systemically administered corticosteroids. In contrast, cromolyn has consistently provided no additive benefit to therapy with inhaled corticosteroids[58-60] or optimal doses of theophylline,[10] and nedocromil in doses of 4 mg[61] and 8 mg[62] four times daily had only a small additive effect in adults being treated with inhaled corticosteroids. In fact, of all the pharmacologic alternatives to theophylline for maintenance therapy for chronic asthma, only salmeterol has been proved to be beneficial in patients who are already receiving an inhaled corticosteroid.[63]

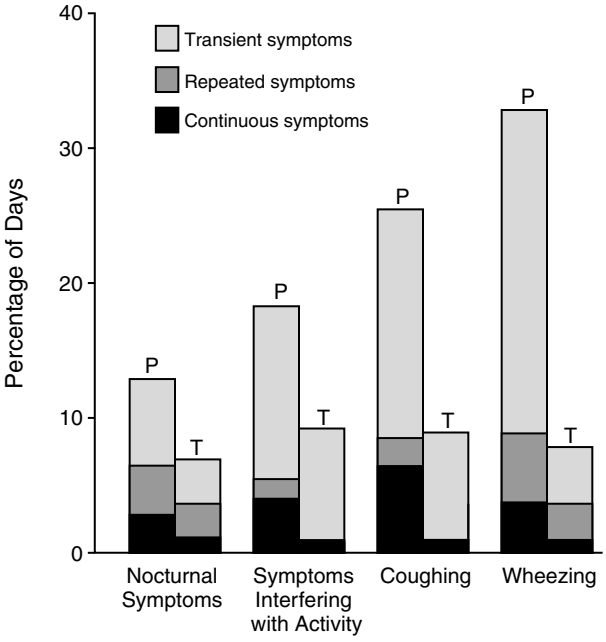


Figure 1. Mean Frequency of Symptoms in 21 Children with Asthma Who Were Receiving a Constant Dose of Beclomethasone Dipropionate and Were Treated in Randomized Sequence for Four Weeks Each with Placebo (P) and Theophylline (T).

The dose of theophylline was individualized to achieve a peak serum concentration of 10 to 20 $\mu$g per milliliter. The dose of beclomethasone averaged 550 $\mu$g daily. Nocturnal symptoms of coughing, wheezing, or dyspnea that disturbed sleep were recorded each morning, and symptoms that interfered with normal activity and any episodes of coughing or wheezing during the day were recorded each evening. Symptoms were graded as absent, transient, repeated, or continuous. In addition to its association with significantly fewer symptoms than placebo, theophylline was also associated with significantly less airway responsiveness to exercise and with the need for significantly fewer interventions with both inhaled $\beta_2$-adrenergic agonists and short courses of oral corticosteroids. Data were adapted from Nassif et al.[11]

## PHARMACODYNAMICS

The efficacy and toxicity of theophylline are closely related to the serum drug concentration. The degree of bronchodilation[28] and the decrease in airway responsiveness to exercise[22] parallel changes in serum concentration. In patients receiving theophylline as monotherapy for chronic asthma, doses providing peak serum concentrations between 10 and 20 $\mu$g per milliliter are the most likely to prevent symptoms and decrease the need for rescue therapy.[3,28,29] However, bronchodilatory, antiinflammatory, and immunomodulatory effects of theophylline occur at lower serum concentrations, which may be adequate for some patients.

Transient effects similar to those of caffeine, such as

Table 1. Dosage Guidelines for Theophylline in Children Older Than 6 Months and Adults Who Have No Risk Factors for Decreased Theophylline Clearance.*

| Variable | Weight-Adjusted and Maximal Dose | Comments | Adjustment to Dose |
|---|---|---|---|
| Initial dose | ~10 mg/kg of body weight/day; maximum, 300 mg/day | If initial dose is tolerated, increase the dose no sooner than 3 days later to the first increment. | |
| First increment | ~13 mg/kg/day; maximum, 450 mg/day | If the first incremental increase is tolerated, increase the dose no sooner than 3 days later to the second increment. | |
| Second increment | ~16 mg/kg/day; maximum, 600 mg/day | Measure the peak serum concentration after at least 3 days at the highest tolerated dose.† | |
| Serum theophylline concentration ($\mu$g/ml) | | | |
| <10 | | | Increase approximately 25%. |
| 10–15 | | | Maintain dose if tolerated. |
| 15.1–19.9 | | | Consider a reduction of approximately 10%.‡ |
| 20–25 | | | Withhold next dose, then resume treatment with next lower dose increment. |
| >25 | | | Withhold next 2 doses, then resume treatment with initial dose or lower dose. |

*For infants 6 weeks to 6 months of age, the initial daily dose is calculated according to the following regression equation: dose (in milligrams per kilogram per day) = (0.2)(age in weeks) + 5.0. Subsequent increases in the dose in this age group should be based on peak serum concentrations measured no sooner than three days after the start of therapy. The guidelines listed use doses that are lower than in previous guidelines[64-66] to account for the most recent assessment of population dose requirements and to minimize the risk of even minor adverse effects. With the use of these guidelines, one to two measurements of serum theophylline are usually sufficient to determine the dose requirement, with annual checks thereafter unless clinical indications suggest the need for more frequent assessment.

†The length of time to the peak serum concentration depends on the rate of absorption, the rate of elimination, and the dosing interval.

‡This decreases the likelihood of side effects due to fluctuations in the absorption or elimination rate that may result in serum concentrations above 20 $\mu$g per milliliter and is especially important for patients who require doses higher than those used in the second increment.

nausea, irritability, and insomnia, occur in some patients with serum theophylline concentrations below 20 $\mu$g per milliliter. Headache and vomiting also occur occasionally. These side effects may be present in up to 50 percent of patients when serum concentrations of 10 to 20 $\mu$g per milliliter are rapidly attained, but they are much less frequent when the initial dose is low and the dose is increased at intervals of no less than three days so that these serum concentrations are reached gradually (Table 1).

Although generally well tolerated when given in appropriate doses, theophylline has the greatest potential of all antiasthmatic drugs for serious toxicity at high serum concentrations. Nausea, diarrhea, vomiting, headache, irritability, and insomnia are common when the serum concentration exceeds 20 $\mu$g per milliliter, and seizures, toxic encephalopathy, hyperthermia, brain damage, and death can occur at high serum concentrations.[67] Hyperglycemia, hypokalemia, hypotension, and cardiac arrhythmias may also occur, especially after acute overdose.[68,69]

A single overdose in a patient who has not previously taken theophylline is unlikely to cause a seizure or encephalopathy unless the peak serum theophylline concentration exceeds 100 $\mu$g per milliliter.[69] A single overdose in a patient who has been taking theophylline regularly may be associated with serious toxic effects at concentrations somewhat lower than 100 $\mu$g per milliliter. After repeated excessive doses, however, serious neurologic effects can occur at even lower serum concentrations, though rarely if ever below 30 $\mu$g per milliliter; patients over 60 years of age appear to be at the greatest risk.[69]

## Pharmacokinetics

Theophylline is rapidly, consistently, and completely absorbed when given in solution or as uncoated tablets that dissolve rapidly.[7] Absorption is somewhat delayed but no less complete when the drug is administered after a meal, and evening doses are absorbed more slowly than morning doses.[70] The rate and sometimes the completeness of absorption are variably decreased with formulations designed for delayed or slow release (Table 2).

Once absorbed, theophylline is distributed predominantly throughout extracellular water, with an apparent volume of distribution of about 0.5 liter per kilogram of body weight in both children and adults. Theophylline freely crosses the placenta and passes into breast milk, although only minor adverse effects have been reported in infants receiving the drug in this manner. In plasma, about 40 percent is bound to protein.[71] Theophylline is predominantly eliminated as metabolites formed by hepatic cytochrome P-450 isoenzymes. *N*-demethylation to 1-methylxanthine and 3-methylxanthine is mediated by cytochrome P-450 1A2, and 8-hydroxylation to 1,3-dimethyluric acid by cytochromes P-450 3A3 and P-450 2E1.[72] Genetic factors, environmental agents, and other drugs that alter the activity of these isoenzymes affect the metabolism of theophylline.

The elimination half-life of theophylline gradually decreases during the first year of life from about 24 hours in term neonates; it ranges from 2 to 10 hours in

Table 2. Absorption Characteristics of Selected Slow-Release Formulations of Theophylline Marketed in the United States.*

| Formulation | Time to Peak Serum Concentration† | Comments |
|---|---|---|
| Capsule | | |
| Slo-bid Gyrocap | 3 to 7 hours after morning dose when given every 12 hours | Can be opened and sprinkled on a spoonful of soft food for children who cannot swallow the capsule; contents must be swallowed without chewing; complete absorption occurs in the presence or absence of food. |
| Theo-24‡ | Variable depending on whether taken in the morning after an overnight fast, after breakfast, or in the evening | Incomplete absorption occurs when taken after an overnight fast; pH-dependent dissolution causes much more rapid and complete absorption when taken after food or in the evening. |
| Tablet | | |
| Theo-Dur | 3 to 7 hours after morning dose when given every 12 hours | Scored tablets can be split without affecting absorption characteristics; complete absorption occurs in the presence or absence of food. |
| Uni-Dur‡§ | 8 to 12 hours after once-daily evening dose | Formulation similar to Theo-Dur tablets but more slowly absorbed; nearly complete absorption occurs in the presence or absence of food. |
| Uniphyl‡ | 8 to 12 hours after once-daily evening dose | Incomplete absorption occurs when taken after overnight fast; more complete absorption occurs when taken after food or in the evening. |

*Data were obtained from Hendeles et al.[70]

†The length of time to the peak concentration is a function of the absorption rate dictated by the formulation, the rate of elimination of the patient, and the dosing interval. For the same product, it will be shorter with multiple doses than after a single dose and shorter when doses are given every 12 hours than when given once daily. The times selected for this table represent the times for a reasonable approximation of the peak serum concentration at the dosing interval most commonly used for the product.

‡Marketed for once-daily dosing, but fluctuations in serum concentration will be greater with this regimen than when given every 12 hours.

§Data on the absorption characteristics of this recently released formulation were obtained from the package insert.

children one to nine years old (mean, approximately 4 hours) and 3 to 16 hours (mean, approximately 8 hours) in adults.[71] As a result, children beyond infancy need weight-adjusted doses of theophylline almost twice those of adults, and the range of doses needed by both children and adults varies at least fourfold.[5,6,64] Despite the large variability in theophylline elimination among patients, variability in individual patients is usually relatively small in the absence of confounding factors, such as drug interactions and physiologic abnormalities that alter the elimination of theophylline.[5,6,73] The limited capacity for degradation of theophylline results in dose-dependent kinetics for elimination. Consequently, changes in the steady-state serum concentration during repeated dosing can be disproportionately larger than the changes in the dose.[5,74]

## Dosage

Because the rate and completeness of absorption vary for different formulations of theophylline,[7,70] only the products known to be completely and consistently absorbed should be prescribed (Table 2). Since the effect produced by theophylline parallels its serum concentration, the formulation selected should also be capable of maintaining stable serum concentrations when taken no more often than twice daily. For patients who are unable to swallow capsules or tablets, the contents of the capsules can be sprinkled on a spoonful of soft food and swallowed without chewing.

In selecting the proper dose of theophylline, one must consider age, variations among patients in the rate of theophylline elimination, and the disproportionate effect of changes in the dose on steady-state serum concentrations. The drug is usually given in two divided doses at 12-hour intervals, although other regimens have been used successfully for selected patients who have persistent nocturnal symptoms. These include a larger evening dose, earlier administration of the evening dose, or a single evening dose to compensate for the lower serum concentrations of theophylline that result from delayed absorption of the evening dose.[70]

The initial dosing regimen should allow tolerance to develop to the minor caffeine-like side effects frequently associated with the initiation of therapy (Table 1). According to an evaluation of the dosing regimen incorporated by the Food and Drug Administration into labeling guidelines from 1978 to 1995, fewer than 3 percent of children and less than 10 percent of adults had minor side effects, and only one or two measurements of the serum concentration were generally needed to determine the appropriate dosage.[64] Other dosing guidelines were subsequently recommended to reduce further the frequency of side effects,[65,66] and the dosage schedule in Table 1 incorporates the findings of a recent assessment of dose requirements for 534 children and adults, in which mean dose requirements were lower than those previously reported (unpublished data).

## Precautions

Although dosage requirements, once established, generally remain stable for extended periods,[5,64] intercurrent illness and drug interactions can alter the elimination of theophylline. Hepatitis, cholestasis, cirrhosis, cardiac decompensation, cor pulmonale, and septic shock can slow the elimination of theophylline and increase the serum concentration if the dose is not reduced.[71] Prolonged fever similarly slows theophylline elimination.[75-77] Although the level or duration of fever that slows the elimination of theophylline is not known, fever must be sustained for slower elimination to result in appreciable accumulation of drug; this is unlikely for fever lasting less than 24 hours. There has been speculation that common viral infections of the respiratory tract, even without sustained fever, can slow the elimination of theophylline; however, respiratory syncytial virus infection in children[78] and rhinovirus infection in adults[79] do not affect

the rate of theophylline elimination. These findings are consistent with extensive clinical experience in young children who have had multiple viral respiratory tract infections while receiving maintenance therapy with theophylline without adverse drug effects.

Several drugs alter the pharmacokinetics of theophylline (Table 3). Cigarette or marijuana smoking, even if passive,[80] increases the elimination of theophylline. Discontinuation of smoking or of medications that increase the elimination of theophylline or the addition of medications that slow theophylline elimination therefore require that the dose of theophylline be lowered or serum concentrations be closely monitored. Conversely, theophylline increases the renal clearance of lithium, which may necessitate an adjustment in the dose of the latter.

Some drug interactions with theophylline do not involve altered pharmacokinetics. Ephedrine[4] and other oral $\beta$-adrenergic agonists[81] are synergistic with theophylline and serve to potentiate adverse effects. In patients receiving theophylline, fluorinated volatile anesthetic drugs (especially halothane) can cause ventricular arrhythmias,[82] and ketamine may lower the seizure threshold.[83] In contrast, theophylline may decrease the efficacy of adenosine in the treatment of cardiac arrhythmias, antagonize the sedative effects of benzodiazepines,[84] and antagonize the neuromuscular-blocking effects of nondepolarizing drugs such as pancuronium.[85]

## Safety

Despite the potential for serious toxicity and the frequency of dosing errors in some institutions,[86] an epidemiologic investigation involving 36,000 ambulatory patients who received 225,000 prescriptions for theophylline identified serious toxic reactions (defined as those requiring hospitalization) only rarely (<1 per 1000 patient-years); the risk was five times greater among elderly patients and those taking cimetidine.[87] Only one child and one adult had theophylline-induced seizures; the serum theophylline concentrations in these two patients were about 60 $\mu$g per milliliter.

Although they are generally not apparent to patients, theophylline has measurable neuropsychological and metabolic effects similar to those associated with caffeine.[88] Transient adverse effects on behavior in children may occur after the initiation of therapy with theophylline,[89] but controlled studies demonstrate that performance on standardized academic achievement tests[90] or objective measures of behavior[91] are not affected. Despite the potential of theophylline to stimulate the central nervous system, the quality of sleep was better and the frequency of apneic episodes was lower during maintenance treatment with theophylline than during therapy with cromolyn in the same asthmatic children.[92]

Growth appears to be positively influenced by theophylline. In one study, the growth rate in children with asthma who were receiving maintenance theophylline therapy was greater than that of nonasthmatic children,[93] and in another study children randomly assigned to receive theophylline grew more rapidly than those receiving inhaled beclomethasone.[56]

## Indications

Medications for asthma include those used to relieve acute symptoms when they occur and those used to prevent symptoms of chronic asthma. The traditional use of theophylline for acute bronchodilation has largely been supplanted by the current generation of inhaled bronchodilators, such as albuterol, which are specific for $\beta_2$-adrenergic–agonist receptors and can safely be given in higher doses than older adrenergic bronchodilators. Although a therapeutic trial of theophylline may be justified in selected patients with inadequate responses to an inhaled $\beta_2$-adrenergic agonist and a systemic corticosteroid, it is predominantly as maintenance therapy for chronic asthma that theophylline deserves serious consideration.

Three indications can be identified for which theophylline provides a useful alternative to other available maintenance medications: primary therapy in cases in which the administration of an inhaled corticosteroid is difficult or cumbersome, as in toddlers and preschool-age children; primary therapy in any patient judged more likely to adhere to a regimen of oral medication than an inhaled regimen; and additive therapy for patients whose asthma is not adequately controlled with conventional doses of an inhaled corticosteroid.

Although the antiinflammatory and immunomodulatory effects of theophylline enhance interest in this familiar medication as preventive therapy, it is the antic-

Table 3. Drug Interactions Likely to Cause at Least a 20 Percent Change in the Rate of Elimination of Theophylline.*

| Drugs That Decrease Theophylline Elimination | Drugs That Increase Theophylline Elimination |
|---|---|
| Alcohol (0.9 g/kg) | Aminoglutethimide |
| Allopurinol (≥600 mg per day) | Carbamazepine |
| Cimetidine | Isoproterenol (intravenous) |
| Ciprofloxacin | Moricizine |
| Clarithromycin | Phenobarbital |
| Disulfiram | Phenytoin |
| Enoxacin | Rifampin |
| Erythromycin | Sulfinpyrazone |
| Estrogen | |
| Fluvoxamine | |
| Interferon | |
| Methotrexate | |
| Mexiletine | |
| Pentoxifylline | |
| Propafenone | |
| Propranolol | |
| Tacrine | |
| Thiabendazole | |
| Ticlopidine | |
| Troleandomycin | |
| Verapamil | |
| Zileuton | |

*When given in their usual doses, drugs that decrease the elimination of theophylline will cause increased steady-state serum concentrations, whereas drugs that increase elimination will decrease steady-state serum concentrations. Drug interactions not otherwise referenced in the text and table were obtained from Hendeles et al.[66]

ipated clinical efficacy and expectations of greater patient adherence to the prescribed regimen that provide justification for its use. Inhaled corticosteroids are convenient, safe, and effective at conventional doses for many patients. Although these can be administered to young children by means of a holding chamber with a flexible, tight-fitting mask, daily therapy in uncooperative infants and toddlers is likely to be trying to the parents, and success in the delivery of the medication will vary. Aerosol corticosteroids for administration by means of an open nebulizer are available outside the United States, and parenteral or nasal preparations have been used in nebulizers by some in the United States. However, delivery by mask results in exposure of the face and eyes to potent topical corticosteroids, and data on long-term safety and efficacy are limited. Administration of cromolyn by nebulizer is a safe alternative for young children, but cromolyn is the most expensive and most time-consuming medication for asthma. There appears to be little indication for the use of metered-dose inhalers for cromolyn or nedocromil, given their lesser efficacy as compared with that of an inhaled corticosteroid in doses of 400 and 800 $\mu$g per day.[94,95] Even among patients who can use a metered-dose inhaler for a corticosteroid, the likelihood of adherence to the regimen is greater with an oral medication (Fig. 2).[96]

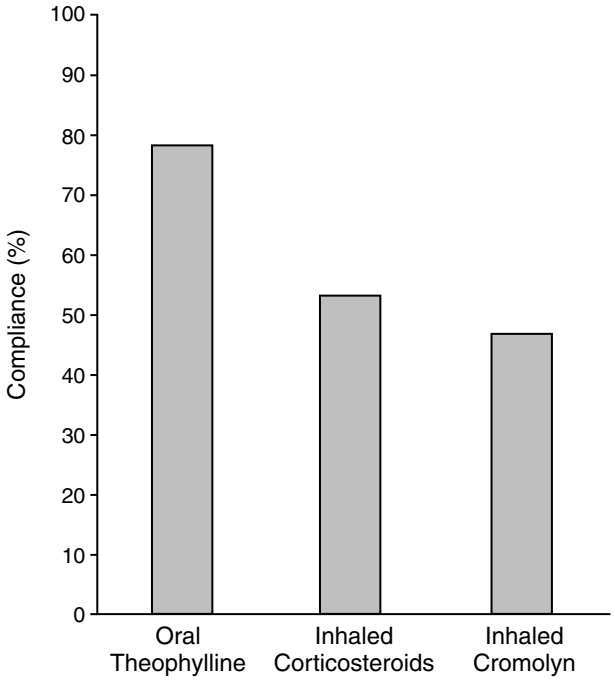


Figure 2. Mean Compliance with the Prescribed Regimen of Maintenance Therapy for Asthma among 119 Randomly Selected Patients, 12 to 65 Years of Age, Who Were Members of a Health Maintenance Organization.

Compliance was determined by dividing the amount of medication used (based on refill rates obtained from pharmacy reimbursement-claims data) by the expected amount (based on the prescribed doses recorded in the patients' charts). Compliance with the inhaled-drug regimens was particularly low among adolescents. Data were adapted from Kelloway et al.[96]

Inhaled corticosteroids alone may provide inadequate control of asthma, even when patients are compliant.[11,14,16,63] Although higher doses of inhaled corticosteroids are safer than the alternatives of poorly controlled asthma or prolonged daily use of systemic corticosteroids, measurable systemic effects, including hypothalamic–pituitary–adrenal suppression, growth suppression, decreased glucose tolerance, and suppression of bone turnover, occur as the dose is increased,[97] and the control of asthma may remain suboptimal.[14,16,63] The addition of theophylline[11,14,16] or inhaled salmeterol[63] can provide more benefit with less risk. Salmeterol is easier to prescribe than theophylline, in that it does not require individualization of the dosage, but the occurrence of hypokalemia at doses twice the usual dose and of a prolonged $QT_C$ interval at 10 times the usual dose suggest a risk of arrhythmias in patients who also take it as a rescue medication during periods of worsening symptoms.[50] Careful instruction and monitoring are needed to ensure that patients use salmeterol properly.

## The Future Role of Theophylline

Theophylline has a narrow therapeutic index, and the development of drugs with greater antiasthmatic effects but less potential for toxicity remains an important goal. A phosphodiesterase inhibitor with greater specificity than theophylline might accomplish this, and clinical trials of phosphodiesterase type IV inhibitors, which have greater antiinflammatory effects than theophylline in asthma,[24] are in progress.[98] Other oral antiasthmatic drugs under investigation are the leukotriene $D_4$–receptor antagonists and 5-lipoxygenase inhibitors. Although those examined so far have only limited efficacy,[99,100] future agents may provide an oral alternative to theophylline. Meanwhile, theophylline continues to be useful in the management of chronic asthma. Doses lower than those that are optimal as monotherapy may be useful when theophylline is used as additive therapy,[16] but data from further trials are needed to determine whether the maximal response is reached at these lower serum concentrations.

Despite the considerable potential benefit of theophylline, its narrow therapeutic index requires skill and knowledge on the part of physicians for safe and effective use of the drug. The role of theophylline today is thus influenced by who the patient is and who is treating the asthma. For the adult and older child who need maintenance medication, early use of an inhaled corticosteroid twice daily in conventional doses is the simplest and safest regimen. For the younger child or any patient who complies poorly with a maintenance regimen of inhaled medication or whose asthma is inadequately controlled with conventional doses of an inhaled corticosteroid, slow-release theophylline offers an alternative that is easy for a parent to administer or for a patient to take but requires that the prescriber have expertise in its use, time to provide adequate instruction, and the ability to provide continuity of care.

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# Theophylline use in asthma

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**INTRODUCTION** — The use of theophylline to treat asthma has undergone several cycles of enthusiasm and unpopularity over the past 50 years. The dissemination of clinical practice guidelines that list theophylline as a "not preferred" alternative, the availability of newer agents, and concerns regarding the risk-benefit ratio of the drug have resulted in infrequent prescribing of theophylline. Nevertheless, its low cost offers an advantage over other long-term maintenance medications that are added to inhaled glucocorticoids, such as montelukast and long-acting beta agonists.

The indications for theophylline in the treatment of asthma and recommendations for its safe use will be discussed here. Overviews of the treatment of acute and chronic asthma are provided elsewhere. (See "Treatment of acute exacerbations of asthma in adults" and "An overview of asthma management".)

**Therapeutic actions** — Though traditionally classified as a bronchodilator, the ability of theophylline to control chronic asthma appears disproportionately greater than is explainable by its modest degree of bronchodilator activity alone [1-7]. Theophylline has antiinflammatory, immunomodulatory, and bronchoprotective effects that potentially contribute to its efficacy as a prophylactic anti-asthma drug [7-14].

Theophylline down-regulates inflammatory and immune cell function in vitro and in vivo in animals with airway inflammation [15,16]. In patients with allergic asthma, it attenuates the late phase increase in airway obstruction and airway responsiveness to histamine, decreases allergen-induced migration of activated eosinophils into the bronchial mucosa, and decreases the sputum eosinophil count [8,9,17]. Moreover, withdrawal of theophylline from patients with severe chronic

asthma receiving high-doses of inhaled glucocorticoid therapy results in increased symptoms of asthma accompanied by an increase in the number of activated cytotoxic T-lymphocytes in the bronchial mucosa and an increase in helper T-lymphocytes in the airway epithelium [7]. The reduction in nocturnal worsening of lung function when theophylline is used is associated with both a decrease in the percentage of neutrophils and a decrease in stimulated leukotriene B4 from macrophages in early morning bronchoalveolar lavage fluid [18]. An in depth review of in vitro and in vivo studies demonstrating the immunomodulatory, anti-inflammatory, and glucocorticoid-sparing effects of theophylline has been published [19].

Although several molecular mechanisms have been proposed to explain the actions of theophylline, the non-specific inhibition of phosphodiesterase that occurs at clinically relevant drug concentrations appears to be the most important. Theophylline increases the intracellular concentration of cyclic nucleotides in airway smooth muscle and inflammatory cells by inhibiting phosphodiesterase-mediated hydrolysis. However, inhibition of specific isozymes may also be important; inhibition of phosphodiesterase type III and type IV relaxes smooth muscles in pulmonary arteries and in airways [20], while antiinflammatory and/or immunomodulatory actions probably result from inhibition of the type IV isozymes [16]. This information has stimulated interest in investigating more specific inhibitors of phosphodiesterase type IV for asthma therapy [21,22]. Theophylline also increases histone deacetylase-2 activity, which may increase glucocorticoid responsiveness in patients with glucocorticoid-resistant severe asthma and in patients with asthma who are cigarette smokers [23].

**INDICATIONS** — There are four clinical circumstances for which theophylline may be considered [24]:

- Additive maintenance therapy in a patient whose asthma is not adequately controlled with conventional doses of inhaled glucocorticoids, or when addition of a long acting beta agonist either provides no benefit or actually causes worsening of control [25].
- Primary maintenance therapy in a patient who is more likely to adhere to an oral than an inhaled regimen and montelukast is not sufficiently effective.
- Primary maintenance therapy when the administration of an inhaled glucocorticoid is difficult or cumbersome (eg, toddlers and preschool-age children) and montelukast is not effective.
- Additive acute therapy in the intensive care unit for patients failing to respond to vigorous use of inhaled ß2-selective agonists in combination with ipratropium and/or intravenous magnesium and systemically administered

glucocorticoids, although evidence for benefit in this situation is lacking. (See 'Additive acute therapy for hospitalized patients' below.)

**Additive maintenance therapy** — Moderate and even high doses of inhaled glucocorticoids (inhaled GC or ICS) may provide inadequate control of moderate asthma, despite optimal compliance and technique [2,5,7,26-29]. Moreover, high doses of inhaled GC may lead to the risk of systemic side effects [30]. (See "Major side effects of inhaled glucocorticoids".)

Randomized, double-blind, controlled trials confirm that the addition of theophylline results in better pulmonary function and symptom control than an increased dose of inhaled GC [2,5,7,28]. (See "Treatment of moderate persistent asthma in adolescents and adults".) Representative studies are reviewed here:

- One study randomly assigned 62 patients to treatment with 800 mcg/day of inhaled budesonide or the combination of theophylline and 400 mcg/day of inhaled budesonide [28]. The doses of theophylline administered were 250 mg or 375 mg, twice daily, for patients weighing <80 kg or ≥80 kg, respectively. The median serum concentration was 8.7 mcg/mL, below the commonly-employed therapeutic range (10-20 mcg/mL). Combination therapy resulted in significantly greater forced expiratory flow in the first second (FEV1) and forced vital capacity (FVC), while there were no differences between the groups in terms of beta-agonist use or peak expiratory flow variability. Adverse events were similar in both treatment groups. The high dose budesonide group exhibited suppressed morning serum cortisol levels at the conclusion of the three month study period, but the clinical significance of this finding is unclear. The authors of this report also estimated that the monthly cost of the combination of low dose budesonide and theophylline was markedly lower than the cost of high dose budesonide or budesonide combined with salmeterol. (See 'Target serum concentration' below.)

- Another trial administered placebo or slow-release theophylline (titrated to maintain serum levels of 10 to 20 mcg/mL) for four weeks to 21 children with chronic asthma who were all receiving an average dose of inhaled chlorofluorocarbon (CFC) beclomethasone of 550 mcg/day (approximately 13 puffs/day) [2]. Compared with placebo, treatment with theophylline produced more symptom-free days (63 versus 42 percent) as well as significant improvements in spirometry and airway responsiveness to exercise. Placebo treatment resulted in twice the frequency of inhaled metaproterenol use and three times the frequency of oral glucocorticoid use (figure 1).

- A crossover study evaluated the consequences of discontinuing theophylline in five adolescents with severe asthma treated with both inhaled and oral

glucocorticoids [5]. There was a marked increase in symptoms, oral prednisone dose, and frequency of beta agonist use beginning within 48 hours of the substitution of placebo for theophylline (figure 2). Two subjects required intensive care admission during placebo treatment, and the Institutional Review Board therefore terminated the study early.

- Withdrawal of theophylline in a double blind fashion from 27 patients with severe chronic asthma, receiving an average dose of 1500 mcg/day (36 puffs/day) of inhaled CFC beclomethasone [7], resulted in a significant increase in asthma symptoms, particularly at night [7]. Theophylline withdrawal was associated with a significant increase in asthma symptoms, particularly at night, and a fall in spirometry and morning peak flow. Withdrawal also resulted in an increase in the number of activated T-lymphocytes in the airway mucosa among the subset of patients who underwent transbronchial biopsy, suggesting that theophylline may have immunomodulatory properties (figure 3).

The ability of theophylline to help control chronic asthma in these and other studies has been disproportionate to its relatively mild bronchodilator activity. For this reason, additional mechanisms of theophylline activity have been postulated [31], including antiinflammatory and immunomodulatory effects [7-9,19] and decreases in airway reactivity to histamine, methacholine, and exercise [10,13]. The former probably result from inhibition of type IV phosphodiesterase isozymes within inflammatory cells [16].

**Compared to other additive therapies** — There are few studies directly comparing the addition of theophylline to the addition of other controller therapies (anti-leukotriene agents, long-acting beta-agonists (LABAs)) in patients receiving inhaled GC therapy. Anti-leukotriene agents and theophylline have the "real-world" advantage of being orally administered rather than inhaled. Many patients find an oral agent simpler to administer than an additional metered dose inhaler, and compliance is greater, on average, with an oral medication [32].

However, only inhaled LABAs, such as salmeterol, have been demonstrated to be superior to theophylline in head-to-head studies, although the difference is small, and there are concerns about the safety of LABAs in some patients [25,33,34]. (See "Beta agonists in asthma: Controversy regarding chronic use".)

- A double blind, double dummy, parallel group study treated 189 patients with moderate-to-severe asthma with four weeks of either slow-release theophylline (dosed twice daily to a serum level of 10 to 20 mcg/mL) or inhaled salmeterol (50 mcg twice daily) [34]. The number of symptom-free nights was significantly greater in the salmeterol group (71 versus 46 percent)

although there were no significant differences in daytime symptoms or peak expiratory flow rate (PEFR). Theophylline caused more gastrointestinal symptoms.

- The differences between theophylline, at therapeutic serum concentrations, and anti-leukotriene agents as additive therapies with inhaled GC, have not been adequately studied. The first head-to-head report found montelukast to have therapeutic advantages, although the study had important methodologic problems [35]. Furthermore, this result would not be predicted by the relatively greater magnitude of clinical benefit reported from theophylline, when the two agents were studied separately as add-on therapy with inhaled GC [5,7,36]. In a subsequent randomized, placebo-controlled parallel trial in 489 adults, neither the addition of low-dose theophylline nor montelukast lowered the event rate in patients with poor asthma control taking inhaled GC [37]. In contrast, in patients not taking inhaled GC, theophylline improved asthma symptoms significantly more than montelukast or placebo. Transient gastrointestinal side effects were more frequent with theophylline. The dose of theophylline in this study was only 300 mg of a 12-hour slow-release formulation daily. Therefore, it is not surprising that added benefit was not observed in patients already taking inhaled GC.

- Theophylline is probably more effective than cromolyn or nedocromil, because unlike theophylline, neither of the chromones has been conclusively shown to provide additional benefit when added to therapy with inhaled GC [38-43]. (See 'Additive maintenance therapy' above and "The use of chromones (cromoglycates) in the treatment of asthma", section on 'Clinical use'.)

Theophylline may be useful to replace a long-acting beta agonist (LABA) added to an inhaled GC when actual worsening of asthma control occurs from apparent loss of bronchoprotective effect, presumably from down regulation of beta2 adrenergic receptors [25].

**Primary maintenance therapy when oral agents are preferred** — Inhaled GC are the most effective long-term maintenance medications for chronic asthma, but their inherent efficacy matters little if patients do not take them consistently enough to receive benefit. A once or twice daily slow-release theophylline regimen may produce better health outcomes in certain patients through improved adherence. Theophylline, as slow release beads sprinkled on soft food, can be tried for young children, in whom administration of inhaled glucocorticoids is difficult.

Several reports indicate that patients adhere poorly to regimens of inhaled maintenance medications. Theophylline appears to cause less difficulty with compliance [32,44].

- One study determined adherence to prescribed maintenance therapy among 119 adults and children with asthma in a Health Maintenance Organization in Minneapolis by comparing pharmacy reimbursement claims data and the chart notation of prescribed therapy [32]. Patients were on average approximately 50 percent adherent with inhaled glucocorticoid or cromolyn regimens but 79 percent adherent with slow-release theophylline. Adherence with inhaled maintenance medications was particularly low among adolescents (figure 4).
- Adherence rates appear to be comparably poor with salmeterol and inhaled GC. In one study, the respective adherence rates were 59 and 56 percent [45].

Anecdotally, we have improved adherence in some patients with moderately severe asthma by treating them with a combination of fluticasone and slow-release theophylline, each given once daily, instead of twice-a-day inhaled GC regimens. In patients whose asthma is not well-controlled, it is advisable to examine prescription refills by calling the patient's pharmacist as a means of assessing compliance before recommending additional maintenance medication [44].

Toddlers and preschool children represent another group in which oral therapy may be advantageous. Inhaled glucocorticoids are the preferred controller medication for children younger than five years with persistent asthma [46]. Inhaled GCs can be administered to young children through a chamber, fitted with a soft mask for the youngest ones. However, many infants and toddlers are uncooperative, making the twice daily administration of medication difficult and the amount of drug delivered to the lungs unreliable. Budesonide has been approved as a nebulizer solution in the United States, but data on long term safety, efficacy, and adherence are limited [47].

In contrast, the administration of slow-release theophylline is a more convenient and considerably less expensive alternative to these medications; the drug may be given by sprinkling medication beads on a spoonful of food twice daily [48].

The efficacy of theophylline in children with mild chronic asthma has been demonstrated in multiple studies to be at least as great as cromolyn [1,49,50], and one randomized crossover trial of cromolyn and theophylline in 28 children with more severe chronic asthma found that patients had significantly more symptom-free days while on theophylline (71 versus 59 percent) without significant differences in side effects [1].

**Additive acute therapy for hospitalized patients** — In general, limited benefit is derived by adding intravenous theophylline, in the form of theophylline or aminophylline (theophylline with ethylenediamine in an 80-85/15-20% ratio), to intensely administered inhaled beta agonists and systemic glucocorticoids for

patients hospitalized with an acute asthma exacerbation [46]. More detailed discussions of the use of theophylline in the management of acute exacerbations of asthma in adults and children are provided separately. (See "Treatment of acute exacerbations of asthma in adults", section on 'Methylxanthines' and "Acute asthma exacerbations in children: Inpatient management", section on 'Methylxanthines'.)

For patients who are on chronic theophylline and unable to take oral medication during an acute exacerbation, the serum level should be assessed and intravenous theophylline administered at a maintenance infusion rate, adjusted if needed to achieve a peak serum concentration of 10 to 20 mg/L (table 1).

**Dosing of IV theophylline** — For patients not previously receiving theophylline, a single intravenous loading dose of theophylline, 5 to 7.5 mg/kg, will provide a peak serum theophylline concentration of about 10 and 15 mcg/ml and may be justified for patients with severe acute symptoms that do not respond rapidly to routine measures. There is minimal risk for serious toxicity with such a dose, and a continuous infusion may then be initiated if obvious clinical improvement results [51] (table 1).

**SAFE USE OF THEOPHYLLINE** — Theophylline has a narrow therapeutic index and wide interpatient variability in clearance. As a result, dosing must be individually titrated to appropriate steady-state serum concentrations in order to achieve maximal benefit and safety. This requires skill and knowledge on the part of the clinician and an ability of patients or parents to follow instructions properly. Failure to adequately monitor theophylline use can lead to potentially fatal drug intoxication. (See "Theophylline poisoning".)

Theophylline is well tolerated and there is little risk of serious toxicity when the drug is administered properly [52]. As an example, one epidemiologic investigation of 36,000 ambulatory patients who received 225,000 prescriptions for theophylline over a nine year period found that the risk of hospital admission due to complications of chronic theophylline use was less than 1 per 1000 patient-years of exposure [53].

Factors that must be considered to maximize the safety of theophylline include proper target serum concentration, appropriate dosage titration, the presence of conditions or factors that affect theophylline metabolism, and proper product and dosing interval selection.

**Target serum concentration** — The efficacy and toxicity of theophylline are closely related to the PEAK serum concentration. In patients receiving theophylline monotherapy, doses providing a PEAK serum concentration of 10 to 20 mg/L (mcg/mL) are best documented to improve symptoms and reduce the need for rescue therapy [54-56]. However, bronchodilatory, antiinflammatory, and

immunomodulatory effects of this drug are detectable at levels as low as 5 mg/L [7,9,56]; in addition, serum concentrations of 5 to 10 mg/L may be adequate for some patients, particularly if they are also receiving inhaled glucocorticoids [19].

We recommend titrating dosage to a PEAK concentration of 10 to 15 mg/L with a theophylline formulation and dosing interval that will not result in large fluctuations between the peak and trough levels. A widely quoted guideline recommends a target serum concentration of 5 to 15 mg/L, but does not specify whether this should be a peak or trough level [46]. Such a distinction is important because fluctuations in serum concentration can be sufficient for a trough concentration in the 5 to 15 mg/L range to result in a peak above 20 mg/L and consequent toxicity [57].

**Initiating and titrating oral therapy** — When beginning theophylline for maintenance therapy, the initial dose should be sufficiently low to avoid transient caffeine-like side effects such as insomnia and irritability. In non-smoking adults without risk factors for reduced theophylline clearance, a starting dose of 10 mg per kg of body weight per day (up to 300 mg for the initial dose) is appropriate in most cases. In obese patients, ideal body weight is used in this calculation. A sustained release product should be used from the beginning.

The dose is then increased, at intervals of three days or more, until the average dose requirements for age are approached (table 2). If a particular dose increase produces unacceptable side effects, the dose should be reduced to that which had been previously tolerated. A single serum concentration measurement is then obtained at the highest tolerated dose, and the final dose is adjusted accordingly (table 2). Fewer than 3 percent of children and 10 percent of adults experience intolerance to theophylline at peak serum concentrations less than 20 mg/L if a slow titration schedule is used, such as the one listed in the table (table 2) [52].

In patients with risk factors for reduced theophylline clearance or in whom the serum concentration cannot be measured in a timely fashion, the maximum daily dose should not exceed 10 mg per kg/day or 400 mg/day [58]. In infants six weeks to six months of age, the initial daily dose in mg/kg can be calculated from the following formula: (0.2 x age in weeks) + 5. Increases beyond the initial dose should be based upon serum theophylline concentration.

Generally only one, and uncommonly two, serum concentration measurements are required to achieve a therapeutic peak concentration [52]. The initial measurement is made at the end of the dose titration schedule (table 2). To properly measure the peak concentration, a blood sample should be obtained 3 to 7 hours after a morning dose of preparations indicated for twice-daily administration, or 8 to 12 hours after preparations with sufficiently slow absorption to permit once daily administration (table 3). In the absence of intercurrent illness associated with

sustained fever or drug interactions, serum concentrations can be expected to remain relatively stable, and repeat measurement in six months for rapidly growing children or one year in other patients is generally sufficient [52].

**Factors affecting metabolism** — Theophylline is metabolized predominately in the liver by the enzyme cytochrome P450 1A2, and to a lesser extent by P450 3A3 and P450 2E1 [58]. Genetic factors, concurrent diseases, environmental agents, and other drugs that alter the activity of these isozymes affect the metabolism of theophylline. When the rate of theophylline metabolism is reduced, the total daily dose must be appropriately decreased to prevent excessive accumulation and toxicity [58].

The following are risk factors for reduced theophylline clearance:

- Age less than 1 or greater than 60.
- Concurrent diseases such as acute pulmonary edema, heart failure, cor pulmonale, fever above 38.9ºC (102ºF) for more than 24 hours, hypothyroidism, liver disease, reduced renal function in infants less than three months of age, and sepsis with multiorgan failure.
- Recent smoking cessation.
- Pregnancy, particularly during the third trimester. (See "Management of asthma during pregnancy".)
- Addition of a drug that inhibits theophylline metabolism (eg, cimetidine, ciprofloxacin, erythromycin, tacrine) or discontinuation of a concurrently administered drug that enhances theophylline metabolism (eg, carbamazepine, rifampin) (table 4A-B). Common drugs that do NOT interact with theophylline are also shown (table 5).

Clinicians can obtain mean values for half-life and total body clearance for the above factors from the tables, which contain the revised FDA labeling guideline for oral theophylline dosage forms (table 4A-B) [58].

**Selection of product and dosing interval** — Slow-release formulations allow a longer dosing interval than rapid release formulations but vary in their rates and completeness of absorption (table 3).

- Food caused a precipitous increase in the rate of absorption and peak concentration with the formulation marketed as Theo-24 [59], whereas taking the formulation identified as Uniphyl on an empty stomach resulted in a marked decrease in absorption [60]. Only products that are completely and consistently absorbed should be selected. We prefer either United States

Federal Drug Administration (FDA) AB-rated generic slow-release tablets or capsules for twice daily dosing, or Uniphyl taken with an evening meal for once daily dosing.

- Capsule formulations are particularly advantageous for preschool-age children because the capsules can be opened and the beads sprinkled on a teaspoonful of food every 12 hours without affecting pharmacokinetics [48].
- For patients with primarily nocturnal symptoms, described strategies have included two-thirds of the total daily dose given in the evening and one-third in the morning, or a single dose given in the evening.

The difference between the peak and trough serum concentrations is a function of the rate of absorption of the product, the dosing interval selected by the clinician, and the rate of theophylline metabolism by the patient [61]. In patients with rapid metabolism, such as children, even a formulation as slowly absorbed as Uniphyl is likely to result in a large difference between the peak and trough, whereas administration of the Uniphyl formulation once-nightly in patients with slower metabolism, as in many adults, may provide acceptable fluctuations between the peak and trough concentrations [60].

**Monitoring** — After initial titration of the dose, we suggest checking the theophylline serum concentration at the estimated peak every 12 months, unless a change in concomitant medications or health status (eg, pregnancy, symptoms of toxicity) dictates a shorter interval. The peak serum concentration varies somewhat with the preparation used, but 4 to 8 hours after a dose is a reasonable estimate for most 12 hour preparations. Products with a claim for 24 hour dosing, taken in the evening, will probably have a peak in the morning.

## SUMMARY AND RECOMMENDATIONS

- Theophylline has bronchodilatory, antiinflammatory, immunomodulating, and bronchoprotective effects. (See 'Therapeutic actions' above.)
- Theophylline remains a useful and inexpensive medication for patients with chronic asthma whose symptoms are not controlled with conventional doses of inhaled glucocorticoids, and patients who cannot take or are poorly compliant with inhaled medications. (See 'Indications' above.)
- The addition of theophylline to inhaled glucocorticoids is more effective than increasing the dose of inhaled glucocorticoids. (See 'Additive maintenance therapy' above.)
- Salmeterol is more effective than theophylline when added to inhaled glucocorticoids, although the differences are not large. More studies are

needed to evaluate the relative efficacy of therapeutic concentrations of theophylline and anti-leukotriene agents as add-on therapies. In patients in whom the addition of a long-acting beta agonist (LABA) to high dose inhaled glucocorticoid does not seem effective, a trial of substituting theophylline for the LABA may be worthwhile. (See 'Compared to other additive therapies' above.)

- Theophylline is not routinely indicated for the treatment of acute severe asthma in the intensive care unit. Intravenous theophylline (as theophylline or aminophylline) may be added when patients with severe acute asthma fail to respond to vigorous use of inhaled albuterol and ipratropium with systemic glucocorticoids, although evidence for this is lacking. (See 'Additive acute therapy for hospitalized patients' above.)
- Safe use of oral theophylline as a maintenance therapy requires initiating treatment at a low dose, measuring a serum concentration to adjust the dose, and reducing the dose in the presence of physiologic states or medications that impair theophylline metabolism. (See 'Safe use of theophylline' above.)
- The absorption characteristics of specific formulations vary considerably, particularly with regards to the effects of food. Familiarity with these details is important. (See 'Selection of product and dosing interval' above.)



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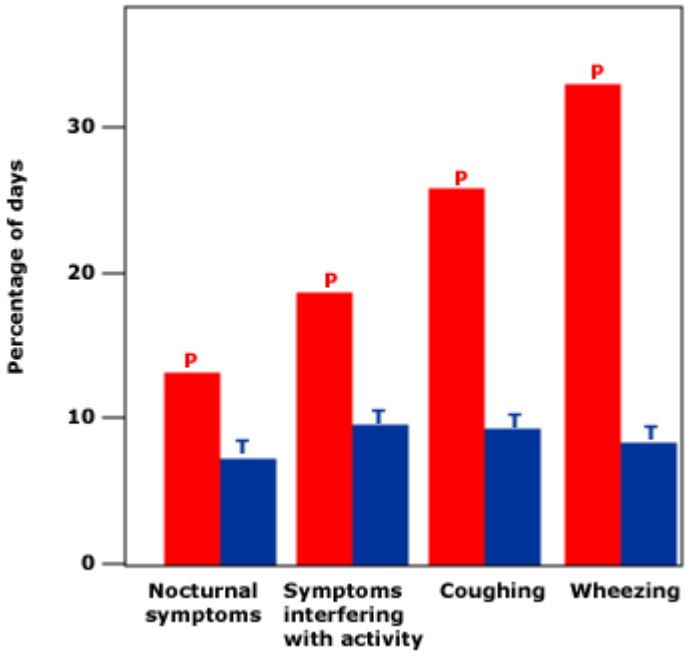
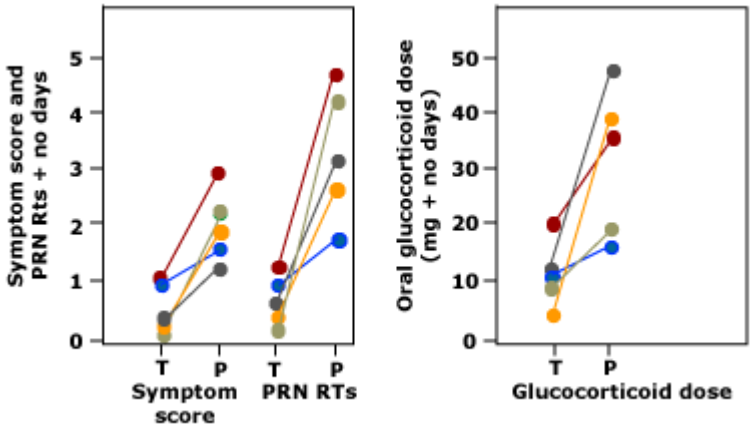
## GRAPHICS

### Addition of theophylline to inhaled glucocorticoids



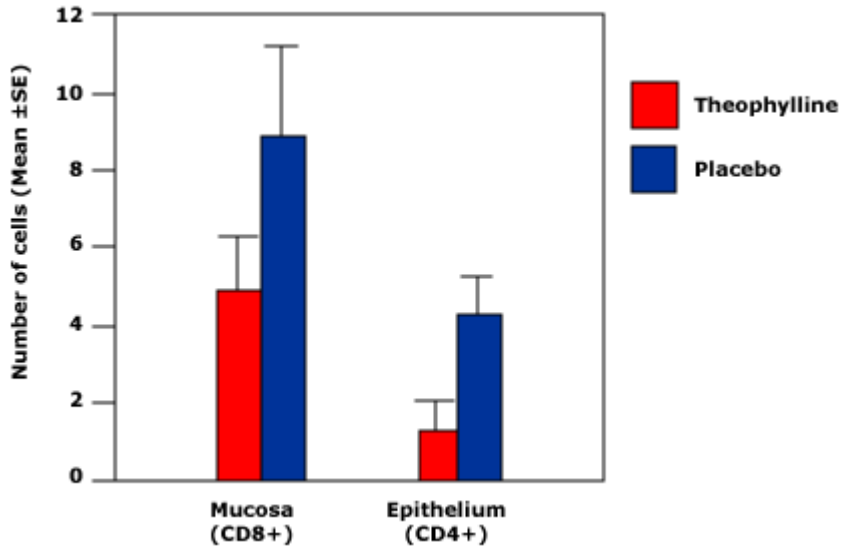

Mean frequency of symptoms in 21 children with asthma who were receiving a constant dose of chlorofluorocarbon (CFC) beclomethasone dipropionate and were treated in randomized sequence for four weeks each with placebo (P) and theophylline (T). The dose of theophylline was individualized to achieve a peak serum concentration of 10 to 20 µg per milliliter. The dose of CFC beclomethasone averaged 550 µg daily. Nocturnal symptoms of cough, wheezing, or dyspnea that disturbed sleep were recorded each morning, and symptoms that interfered with normal activity and any episodes of cough or wheezing during the day were recorded each evening. *Redrawn from: Weinberger M, Hendeles L, N Engl J Med 1996; 334:1380.*

## The effect of abrupt withdrawal of theophylline in five children with glucocorticoid-dependent asthma



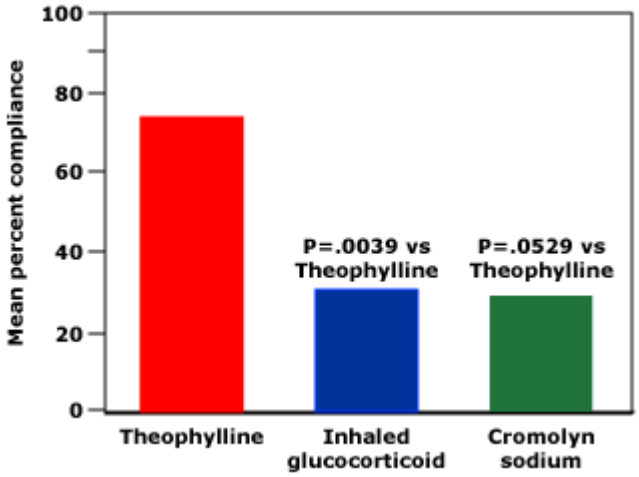

The left panel represents the average daily scores for symptoms of asthma and the number of extra respiratory treatments (RT) with bronchodilator. The right panel shows the average daily dose of prednisone required to treat the patient during theophylline (T) and placebo (P) treatment periods. *Redrawn from Brenner, M, Berkowitz, R, Marshall, N, Strunk, RC, Clin Allergy 1988; 18:143.*

## Effect of withdrawing theophylline on airway lymphocytes




Change in activated lymphocyte counts in bronchial biopsy specimens of 8 patients in whom theophylline was abruptly withdrawn. Withdrawal of theophylline to placebo was associated with increased activated lymphocytes in bronchial biopsy specimens. *Figure drawn from data published in Kidney, J, Dominguez, M, Taylor, PM, et al. Am J Respir Crit Care Med 1995; 151:1907.*

## Compliance with medication regimens in asthma




Adherence to inhaled glucocorticoids, slow-release theophylline, and cromolyn among 14 adolescents in an HMO. Adherence was determined by dividing the amount of medication used (based on refill rates obtained from pharmacy reimbursement-claims data) by the expected amount (based on the prescribed doses recorded in the patients' charts). Adherence with the inhaled-drug regimens was particularly low among adolescents. *Data from Kelloway, JS, Wyatt, RA, Adlis, SA, Arch Intern Med 1994; 154:1349.*

## Infusion rates for IV theophylline

| Patient age/characteristics | Infusion rate |
|---|---|
| Neonates (postnatal age up to 24 days) | 1 mg/kg q 12 h |
| Neonates (postnatal age beyond 24 days) | 1.5 mg/kg q 12 h |
| Infants (6 to 52 weeks) | mg/kg/hr = (0.008) (age in weeks) + 0.21 |
| Young children (1 to 9 yr) | 0.8 mg/kg/hr |
| Adolescents (12 to 16 yr) who smoke cigarettes or marijuana smokers | 0.7 mg/kg/hr |
| Adolescent nonsmokers | 0.5 mg/kg/hr |
| Adult smokers | 0.5 mg/kg/hr |
| Adult nonsmokers | 0.4 mg/kg/hr |
| Patients with cardiac decomp, cor pulmonale, or liver dysfunction | 0.2 mg/kg/hr |

These rates are suggested for use after the initial loading does has been administered.

**Maintenance dosage guidelines for theophylline in children older than six months and adults who have no risk factors for decreased theophylline clearance***

| Variable | Weight-adjusted and maximal dose | Comments | Adjustment to dose |
|---|---|---|---|
| Initial dose | ~10 mg/kg of body weight/day; maximum, 300 mg/day | If initial dose is tolerated, increase the dose no sooner than 3 days later to the first dose increase. | |
| First dose increase | ~13 mg/kg/day; maximum 450 mg/day | If the first dose increase is tolerated, increase the dose no sooner than 3 days later to the second dose increase. | |
| Second dose increase | ~16 mg/kg/day; maximum 600 mg/day | Measure the peak serum concentration after at least 3 days at the highest tolerated dose.• | |
| Serum theophylline concentration (µg/mL) | | | |
| <10 | | | Increase approximately 25 percent. |
| 10 to 15 | | | Maintain dose if tolerated. |
| 15.1 to 19.9 | | | Consider a reduction of approximately 10 percent. |

| | | | |
|---|---|---|---|
| 20 to 25 | | | Withhold next dose, then resume treatment with next lower dose level. |
| >25 | | | Withhold next 2 doses, then resume treatment with initial dose or lower dose. |

* For infants 6 weeks to 6 months of age, the initial daily dose is calculated according to the following regression equation: dose (in milligrams per kilogram per day) = (0.2) (age in weeks) + 5.0. Subsequent increases in the dose in this age group should be based on peak serum concentrations measured no sooner than three days after the start of therapy.

• The length of time to the peak serum concentration depends on the rate of absorption, the rate of elimination, and the dosing interval.

Δ This decreases the likelihood of side effects due to fluctuations in the absorption or elimination rate that may result in serum concentrations above 20 µg per milliliter and is especially important for patients who require doses higher than those used in the second dose increase. *Adapted from Weinberger, M, Hendeles, L, N Engl J Med 1996; 334:1380.*

**Absorption characteristics of selected slow-release formulations of theophylline marketed in the United States**

| Formulation | Time to peak serum concentration | Comments |
|---|---|---|
| Theo-24 | Variable depending on whether taken in the morning after an overnight fast, after breakfast, or in the evening. | Incomplete absorption occurs when taken after an overnight fast; pH-dependent dissolution causes much more rapid (ie, dose-dumping) and complete absorption when taken after food or in the evening. |
| Generic SR tablets | 3 to 7 hours after morning dose when given every 12 hours. | Scored tablets can be split without affecting absorption characteristics; complete absorption occurs in the presence or absence of food. |
| Generic SR capsules | 3 to 7 hours after morning dose when given every 12 hours. | Can be opened and sprinkled on a spoonful of soft food for children who cannot swallow the capsule; contents must be swallowed without chewing; complete absorption occurs in the presence or absence of food. |
| Uniphyl | 8 to 12 hours after once-daily evening dose. | Incomplete absorption occurs when taken after overnight fast; more complete absorption occurs when taken after food or in the evening. |

The times selected for this table represent the times for a reasonable approximation of the peak serum concentration at the dosing interval most commonly used for the product. *Adapted from Weinberger, M, Hendeles, L, N Engl J Med 1996; 334:1380.*

## Clinically significant drug interactions with theophylline

| Drug | Type of interaction | Effect on theophylline serum concentrations or pharmacologic effect |
|---|---|---|
| Adenosine | Theophylline blocks adenosine receptors | Higher doses of adenosine may be required to achieve desired anti-arrhythmic effect |
| Alcohol | A single large dose of alcohol (3 ml/kg of whiskey) decreases theophylline clearance for up to 24 hours | 33 percent increase |
| Allopurinol | Decreases theophylline clearance at allopurinol doses ≥600 mg/day | 25 percent increase |
| Aminoglutethimide | Increases theophylline clearance by induction of microsomal enzyme activity | 25 percent decrease |
| Carbamazepine | Similar to aminoglutethimide | 30 percent decrease |
| Cimetidine | Decreases theophylline clearance by inhibiting cytochrome P450 1A2 | 70 percent increase |
| Ciprofloxacin | Similar to cimetidine | 40 percent increase |
| Clarithromycin | Similar to erythromycin | 25 percent increase |
| Diazepam | Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors | Larger diazepam doses may be required to produce desired level of sedation |
| | | Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression |

| | | |
|---|---|---|
| Disulfiram | Decreases theophylline clearance by inhibiting hydroxylation and demethylation | 50 percent increase |
| Enoxacin | Similar to cimetidine | 300 percent increase |
| Ephedrine | Synergistic CNS effects | Increased frequency of nausea, nervousness, and insomnia |
| Erythromycin | Erythromycin metabolite decreases theophylline clearance by inhibiting cytochrome P450 3A3 | 35 percent increase. Erythromycin steady-state serum concentrations decrease by a similar amount |
| Estrogen | Estrogen-containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown | 30 percent increase |
| Flurazepam | Similar to diazepam | Similar to diazepam |
| Fluvoxamine | Similar to cimetidine | Similar to cimetidine |
| Halothane | Halothane sensitizes the myocardium to catecholamines; theophylline increases release of endogenous catecholamines | Increased risk of ventricular arrhythmias |

*Redrawn from Hendeles, L, Jenkins, J, Temple, R, Pharmacotherapy 1995; 15:409.*

## Clinically significant drug interactions with theophylline

| Drug | Type of interaction | Effect on theophylline serum concentrations or pharmacologic effect |
|---|---|---|
| Interferon, human recombinant alpha-A | Decreases theophylline clearance | 100 percent increase |
| Isoproterenol (IV) | Increases theophylline clearance | 20 percent decrease |
| Ketamine | Pharmacologic | May lower theophylline seizure threshold |
| Lithium | Theophylline increases lithium renal clearance | Lithium dose required to achieve a therapeutic serum concentration increased an average of 60 percent |
| Lorazepam | Similar to diazepam | Similar to diazepam |
| Methotrexate (MTX) | Decreases theophylline clearance | 20 percent increase after low-dose MTX, higher dose MTX may have a greater effect |
| Mexiletine | Similar to disulfiram | 80 percent increase |
| Midazolam | Similar to diazepam | Similar to diazepam |
| Moricizine | Increases theophylline clearance | 25 percent decrease |
| Pancuronium | Theophylline may antagonize non-depolarizing neuromuscular blocking effects; possibly due to phosphodiesterase inhibition | Larger dose of pancuronium may be required to achieve neuromuscular blockade |
| Pentoxifylline | Decreases theophylline clearance | 30 percent increase |

| | | |
|---|---|---|
| Phenobarbital (PB) | Similar to aminoglutethimide | 25 percent decrease after more than two weeks of concurrent PB |
| Phenytoin | Phenytoin increases theophylline clearance by increasing microsomal enzyme activity | Serum theophylline and phenytoin concentrations decrease about 40 percent |
| | Theophylline decreases phenytoin absorption | |
| Propafenone | Decreases theophylline clearance and pharmacologic interaction | 40 percent increase. Beta-2-blocking effect may decrease efficacy of theophylline |
| Propranolol | Similar to cimetidine and pharmacologic interaction | 100 percent increase. Beta-2-blocking effect may decrease efficacy of theophylline |
| Rifampin | Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity | 20 to 40 percent decrease |
| Sulfinpyrazone | Increases theophylline clearance by increasing demethylation and hydroxylation. Decreases renal clearance of theophylline | 20 percent decrease |
| Tacrine | Similar to cimetidine, also increases renal clearance of theophylline | 90 percent increase |
| Thiabendazole | Decreases theophylline clearance | 190 percent increase |
| Ticlopidine | Decreases theophylline clearance | 60 percent increase |
| Troleandomycin | Similar to erythromycin | 33 to 100 percent increase depending on troleandomycin dose |

| | | |
|---|---|---|
| Verapamil | Similar to disulfiram | 20 percent increase |
| Zafirlukast | Mechanism not studied; theophylline decreases either bioavailability or clearance of zafirlukast. Zafirlukast has no effect on theophylline clearance | Zafirlukast blood levels decrease an average of 40 percent, which is likely to render it ineffective |
| Zileuton | Zileuton inhibits cytochrome P-450 1A2 and, thus, decreases theophylline clearance | 100 percent increase |

*Redrawn from Hendeles, L, Jenkins, J, Temple, R, Pharmacotherapy 1995; 15:409.*

## Drugs that have been documented NOT to interact with theophylline or NOT to have clinically important interactions with theophylline

| | |
|---|---|
| Albuterol, systemic and inhaled | Mebendazole |
| Amoxicillin | Medroxyprogesterone |
| Ampicillin, with or without sulbactam | Methylprednisolone |
| Atenolol | Metronidazole |
| Azithromycin | Metoprolol |
| Caffeine, dietary ingestion | Nadolol |
| Cefaclor | Nifedipine |
| Co-trimoxazole (trimethoprim and sulfamethoxazole) | Nizatidine |
| Diltiazem | Norfloxacin |
| Dirithromycin | Ofloxacin |
| Enflurane | Omeprazole |
| Famotidine | Paroxetine |
| Felodipine | Prednisone, prednisolone |
| Fluoxetine | Ranitidine |
| Finasteride | Rifabutin |
| Hydrocortisone | Roxithryomycin |
| Isoflurane | Sertraline |
| Isoniazid | Sorbitol (purgative doses do not inhibit theophylline absorption) |
| Isradipine | Sucralfate |
| Influenza vaccine | Terbutaline, systemic |
| Ketoconazole | Terfenadine |
| Lomefloxacin | Tetracycline |
| | Tocainide |

*Redrawn from Hendeles, L, Jenkins, J, Temple, R, Pharmacotherapy 1995; 15:409.*